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Etiology of Sporadic Acute Viral Hepatitis in Taiwan: The Role of Hepatitis C Virus, Hepatitis E Virus and GB Virus-C/Hepatitis G Virus in an Endemic Area of Hepatitis A and B

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The etiology of sporadic acute hepatitis was studied in 334 consecutive patients from Taiwan (237 men and 97 women, aged 16–81 years), with emphasis on the role of hepatitis C virus (HCV), hepatitis E virus (HEV), and GB virus-C/hepatitis G virus (GBV-C/HGV) in acute non-A, non-B (NANB) hepatitis and in HBsAg carriers with superimposed acute hepatitis. According to the conventional diagnostic criteria, there were 12 cases (3.6%) of acute hepatitis A, 17 cases (5.1%) of acute hepatitis B, 128 cases (38.3%) of acute NANB hepatitis, and 177 cases (53.0%) of acute hepatitis in HBsAg carriers (those who were HBsAg positive but IgM anti-HBc negative). Among 128 cases of acute NANB hepatitis, 70 (54.7%) had acute hepatitis C (HCV RNA positive), 5 (3.9%) had acute hepatitis E (IgM anti-HEV positive), and the other 53 (41.4%) were presumably acute hepatitis non-A-E. The prevalence of acute hepatitis A, B, E, and non-A-E showed no significant sex difference, whereas acute hepatitis C was significantly more prevalent in females. The prevalence of acute hepatitis A and B decreased and that of acute hepatitis C increased significantly with increasing age. In contrast, acute hepatitis E and non-A-E showed no significant age predominance. Of 177 HBsAg carriers with acute hepatitis, 64 (36.1%) demonstrated non-B hepatotropic virus superinfection, with HCV being the most common (60.9%), followed by hepatitis D, E, and A viruses, and the other 55 (31.1%) and 58 (32.8%) were presumed to have acute exacerbation of chronic hepatitis B or superimposed acute hepatitis non-A-E, respectively. Serum GBV-C/HGV RNA was detected in 3–4% of acute hepatitis non-A-E cases, suggesting its limited role in these cases. ***J. Med. Virol. 58:154–159, 1999.***

KEY WORDS: acute hepatitis non-A-E; HCV RNA; IgM anti-HEV

INTRODUCTION

The etiology of acute viral hepatitis may vary considerably with different age, sex, ethnic, and geographic origins [Dienstag et al., 1977; Norkrans et al., 1978; Mathiesen et al., 1979; Caredda et al., 1981; Chan et al., 1981; Farrow et al., 1981; Liaw et al., 1983]. Taiwan is an area with endemic hepatitis A virus (HAV) and hepatitis B virus (HBV) infection. Most adults in this area have been infected with HAV and HBV (90–98% and 85–90% of adults in the general population had serological markers of HAV and HBV, respectively) [Wu et al., 1980; Sung et al., 1984]. In keeping with these epidemiological data, our previous studies in Taiwan have shown that only about 10% of sporadic acute viral hepatitis cases could be attributed to acute HAV or HBV infection, whereas 20–30% of the cases were presumed to be due to acute non-A, non-B (NANB) hepatitis and the remaining 60% of cases were hepatitis B surface antigen (HBsAg) positive but immunoglobulin M (IgM) antibody against hepatitis B core antigen (IgM anti-HBc) negative, and thus indeed were previously unrecognized HBsAg carriers with acute exacerbation of underlying chronic HBV infection or viral superinfection [Chu et al., 1988]. Serological markers for infections due to hepatitis C virus (HCV) and hepatitis E virus (HEV), both previously

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categorized as NANB hepatitis viruses, are now recognized. It seems timely to reevaluate the etiology of sporadic acute viral hepatitis in this endemic area of HAV and HBV, with special emphasis on the role of HCV and HEV in acute NANB hepatitis and in HBsAg carriers with superimposed acute hepatitis.

Recently, a new transmissible agent, the GB virus-C (GBV-C) has been identified [Simons et al., 1995]. This virus belongs to the *Flaviviridae* family and presents notable sequence similarity with another agent, the hepatitis G virus (HGV), identified subsequently in an independent laboratory [Linen et al., 1996]. GBV-C and HGV are different isolates of the same virus [Zuckerman, 1996]. High prevalence rates of GBV-C/HGV have been recorded in patients exposed to blood and blood products, drug addicts, patients on hemodialysis, and in patients with acute and chronic liver disease [Simons et al., 1995; Dawson et al., 1996; Linnen et al., 1996; Karayiannis and Thomas, 1997]. However, the information concerning the role of GBV-C/HGV infection in acute and chronic viral hepatitis is still rather limited. GBV-C/HGV RNA was detected in about 10% of patients with a diagnosis of sporadic acute hepatitis non-A-E in most studies from western countries [Linnen et al., 1996; Dawson et al., 1996; Alter et al., 1997], but was detected in 39% of patients with acute hepatitis of unknown etiology in one study from Italy [Fiordalisi et al., 1996]. The prevalence and the pathogenic role of GBV-C/HGV in sporadic acute hepatitis non-A-E and in HBsAg carriers with superimposed acute hepatitis of undetermined cause in Taiwan also need to be fully elucidated.

MATERIALS AND METHODS

Patients

In a 2-year period from July 1995 to June 1997, a consecutive series of 334 adult patients with sporadic acute viral hepatitis were admitted to the Liver Unit, Chang Gung Memorial Hospital and Medical College, a 3,500-bed medical center in northern Taiwan. The clinical diagnosis of acute viral hepatitis was based on the lack of previous history of chronic liver disease, the discrete onset of signs and symptoms, a rise in serum aminotransferase activity of at least 10 times of the normal value, and the exclusion of other causes of liver disease. All patients denied history of blood transfusion, tattooing, acupuncture, surgery, or dental procedure within 6 months before the onset of illness. No patients admitted homosexual activity or intravenous drug abuse. Of these 334 patients, 237 were men and 97 were women, ages ranged from 16 to 81 years.

Serological Tests

All patients had serum samples collected within 4 weeks after the onset of illness for serological tests. The serodiagnosis of acute viral hepatitis included a panel of serological and virological markers: IgM antibody against HAV (IgM anti-HAV); HBsAg, IgM anti-HBc, anti-HCV, IgG and IgM antibodies against HDV (IgM and IgG anti-HDV); IgM antibody against HEV (IgM anti-HEV); IgM antibody against cytomegalovirus (IgM anti-CMV); and IgM antibody against Epstein-Barr virus capsid antigen (IgM anti-EBV). The serum samples were stored unthawed at −70°C for assay for HBV DNA, HCV RNA, and GBV-C/HGV RNA.

Serum IgM anti-HAV, HBsAg, IgM anti-HBc, and IgG anti-HDV were assayed using commercially available radioimmunoassay kits (HAVAB-M, Ausria II, Corab-M, anti-delta, Abbott Laboratories, North Chicago, IL). IgM anti-CMV was assayed by enzyme immunoassay (CMV IgM, Merck, Germany). IgM anti-EBV was assayed by indirect immunofluorescence (EBV IgM, Gull, Utah). IgM anti-HDV was assayed using enzyme immunoassay kits (Deltassay IgM, Cambridge Biotect Limited, Dublin, Ireland). Anti-HCV were assayed by second generation enzyme immunoassays (UBI-HCV-EIA, United Biochemical Inc., Lake Success, NY) that were based on synthetic peptides derived from immunodominant regions of both capsid and nonstructural HCV proteins. IgM anti-HEV was detected using an enzyme-liked immunosorbent assay (Genelabs, Inc., Redwood City, CA). HBV DNA was assayed by spot hybridization using ^{32}P-labeled cloned HBV DNA. The detection sensitivity was 0.5 pg per 50 μl [Chu et al., 1985]. HCV RNA was assayed using a sensitive reverse transcription-polymerase chain reaction (PCR) method (AMPLICOR HCV test, Roche Diagnostic system, Inc., NJ). The detection sensitivity of this assay is 10^1–10^2 copies per milliliter. GBV-C/HGV RNA was detected by PCR with the specific primers that were derived from the 5′ untranslated region of GBV-C/HGV, as described by Kao et al. [1997a].

Diagnostic Criteria

Patients were diagnosed as having acute hepatitis A if IgM anti-HAV was positive, acute hepatitis B if IgM anti-HBc was positive, and acute hepatitis E if IgM anti-HEV was positive. The presence of IgM anti-HDV, however, could not distinguish between acute and chronic HDV infection. Because the titers of IgG anti-HDV tended to be low in acute HDV infection but high in chronic HDV infection, the present study adopted the criteria of positive IgM anti-HDV with IgG anti-HDV in titers of less than 1:100 to diagnose acute hepatitis D [Hoofnagle, 1983].

The serodiagnosis of acute hepatitis C was particularly difficult. The presence of anti-HCV in initial acute-phase serum samples failed to distinguish between acute and chronic HCV infection. On the other hand, anti-HCV might develop relatively late in the course of infection, and convalescent-phase serum samples (>6 months after the onset of illness) were needed for diagnosis of acute hepatitis C. Furthermore, some patients were diagnosed as having acute hepatitis C solely on the basis of positive HCV RNA without seroconversion of anti-HCV. Of the 106 patients with acute hepatitis C diagnosed by Alter et al. [1992], 63 (59%) were anti-HCV positive in initial acute-phase serum samples, 30 (28%) developed anti-HCV more than 6 months after the onset of illness, and 13 (12%) were

TABLE I. Etiology of Sporadic Acute Viral Hepatitis in Taiwan

Etiology	Male	Female	Total
Acute hepatitis A	8 (3.4%)[a]	4 (4.1%)[a]	12 (3.6%)
Acute hepatitis B	10 (4.2%)[b]	7 (7.2%)[b]	17 (5.1%)
Acute hepatitis C	37 (15.6%)[c]	33 (34.0%)[c]	70 (21.0%)
Acute hepatitis E	5 (2.1%)[d]	0 (0%)[d]	5 (1.5%)
Acute hepatitis non-A-E	34 (14.3%)[e]	19 (19.6%)[e]	53 (15.9%)
Acute hepatitis in HBsAg carrier	143 (60.3%)[f]	34 (35.1%)[f]	177 (53.0%)
Total	237 (100%)	97 (100%)	334 (100%)

[a,b,d,e,]$P > .2$; [c,f]$P < .001$ by chi-square test with Yates' correction.

HCV RNA positive without seroconversion of anti-HCV. It is noteworthy that HCV RNA was positive in every patient of Alter's series who was anti-HCV positive during the acute phase or who developed anti-HCV during the convalescent phase [Alter et al., 1992]. Based on these findings, it seems that a test of HCV RNA in a single acute-phase serum sample can diagnose acute hepatitis C in every patients of the Alter series. Because it was difficult to collect convalescent-phase serum samples from all of our study patients, in the present study acute hepatitis C was diagnosed if the acute-phase serum samples were HCV RNA positive, with or without anti-HCV, though the possibility of chronic hepatitis C with acute exacerbation or superimposed unrelated form of acute hepatitis cannot be excluded.

Patients were considered to have acute hepatitis non-A-E if HBsAg was negative and evidence of acute hepatitis A, B, C, D, and E was excluded. Patients who were HBsAg positive but IgM anti-HBc negative were considered as chronic HBsAg carriers with acute exacerbation of underlying chronic HBV infection or viral superinfection [Hoofnagle, 1983; Chu et al., 1989]. Of these patients, acute HAV, HCV, HDV, or HEV superinfection was diagnosed according to the criteria as described above. Acute exacerbation of the underlying chronic HBV infection was suspected when there was no evidence of acute HAV, HCV, HDV, or HEV infection, and HBV DNA was positive by spot hybridization, though the presence of HBV DNA in itself was not diagnostic of this event. Patients were presumed to have superimposed acute hepatitis non-A-E if there was no evidence of HAV, HCV, HDV, or HEV infection, and HBV DNA was also negative by spot hybridization, though the possibility of acute reactivation of chronic HBV infection with early clearance of HBV viremia could not be excluded completely [Liaw et al., 1988].

Finally, the presence of GBV-C/HGV RNA in the study patients was correlated with the established causes of acute viral hepatitis.

Statistical Analyses

Statistical analysis was conducted using chi-square test with Yates' correction and chi-square test for trend where appropriate.

RESULTS

Of the 344 patients with sporadic acute viral hepatitis, 12 (3.6%) had acute hepatitis A, 17 (5.1%) had acute hepatitis B, 128 (38.3%) had acute hepatitis NANB (IgM anti-HAV, HBsAg, IgM anti-HBc, IgM anti-CMV, and IgM anti-EBV all negative), and the remaining 177 (53.0%) were cases of acute hepatitis in chronic HBsAg carriers. Of the 128 cases with acute hepatitis NANB, 70 (54.7%) had acute hepatitis C, 5 (3.9%) had acute hepatitis E, and the other 53 (41.4%) had acute hepatitis non-A-E (Table I). The prevalence of acute hepatitis A, B, E, and non-A-E showed no significant sex difference. In contrast, acute hepatitis C was significantly more prevalent in females, whereas acute hepatitis in HBsAg carriers was significantly more prevalent in males (Table I). The age-specific prevalence of acute hepatitis A, B, C, E, non-A-E, and acute hepatitis in HBsAg carriers is shown in Figure 1. The prevalence of acute hepatitis A and B decreased significantly and that of acute hepatitis C increased significantly with increasing ages ($P < .01$, $< .001$, and $< .001$, respectively, by chi-square test for trend). The prevalence of acute hepatitis E and non-A-E was 0–2% and 15–20%, respectively, with no significant age predominance ($P > .2$, respectively, by chi-square test for trend). Acute hepatitis in HBsAg carriers was the main etiology of acute hepatitis, accounting for 40–60% of cases in each age group.

Among the 177 HBsAg carriers with acute hepatitis, 64 (36.1%) demonstrated serological markers of acute non-B hepatotropic virus superinfection, with HCV being the most common, followed by HDV, HEV, and HAV, without any sex difference (Table II). Of the remaining 113 HBsAg carriers with acute hepatitis, 55 were HBV DNA positive by spot hybridization and were presumed to have acute exacerbation of chronic HBV infection and the other 58 were suspected to have superimposed acute hepatitis non-A-E (Table II).

Serum GBV-C/HGV RNA was positive in about 11–12% of acute hepatitis C cases or HBsAg carriers with superimposed acute hepatitis C, 5–6% of acute hepatitis B or D cases, and 3–4% of acute hepatitis non-A-E cases, but was rarely detected in cases with other causes of acute hepatitis (Table III).

DISCUSSION

The present results revealed that only 31% (104/334) of sporadic acute viral hepatitis in Taiwan had simple acute hepatotropic virus infection (Table I), though another 19% (64/334) had acute non-B hepatotropic virus infection superimposed upon chronic HBV infection (Table II). About 4% and 5% of adult sporadic acute

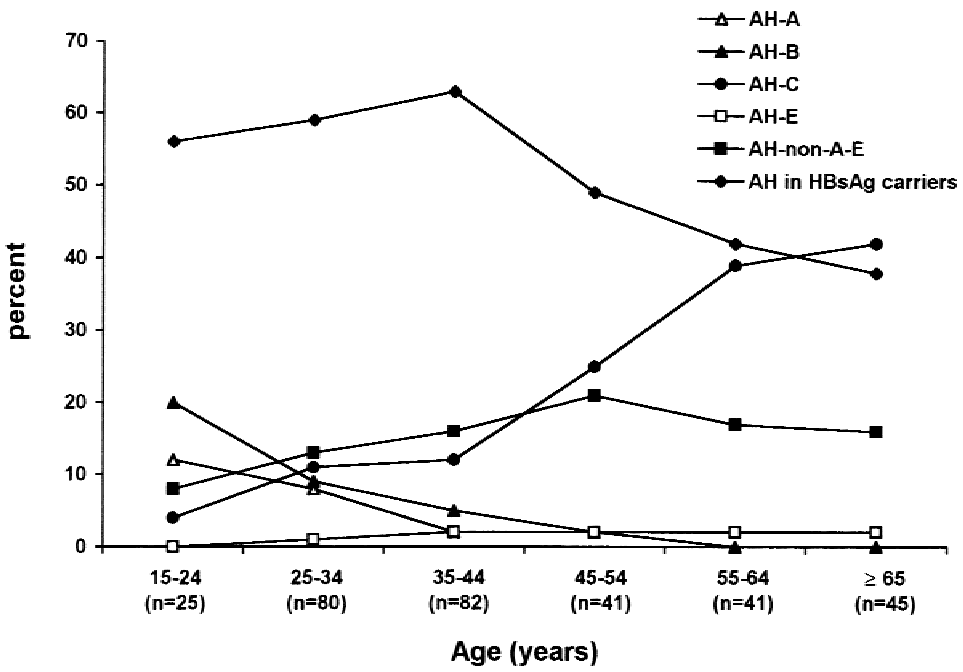

Fig. 1. Age-specific etiological analysis of 334 adult patients with sporadic acute viral hepatitis in Taiwan. AH, acute hepatitis.

TABLE II. Etiology of Acute Hepatitis Superimposed Upon Chronic HBsAg Carriers

Etiology	Male	Female	Total
Hepatitis A superinfection	2 (1.1%)	0	2 (1.1%)
Hepatitis C superinfection	27 (18.9%)	8 (23.5%)	35 (19.8%)
Hepatitis D superinfection	14 (9.8%)	3 (8.8%)	17 (9.6%)
Hepatitis E superinfection	6 (4.2%)	0	6 (3.4%)
Hepatitis C and D superinfection	4 (2.5%)	0	4 (2.3%)
Others			
Hepatitis B virus DNA positive	42 (29.4%)	13 (38.2%)	55 (31.1%)
Hepatitis B virus DNA negative	48 (33.6%)	10 (29.4%)	58 (32.8%)
Total	143 (100%)	34 (100%)	177 (100%)

$P > .2$ for all comparisons between males and females.

viral hepatitis cases in the present series could be attributed to acute hepatitis A and B, respectively, without any sex difference (Table I). The prevalence of acute hepatitis A and B correlated significantly with the age of patients. The prevalence of acute hepatitis A was 12%, 8%, and ≤2% in patients aged 15–24, 25–34, and ≥ 35 years, respectively (Fig. 1). These findings were in keeping with the epidemiological background of HAV infection in Taiwan, where only 10%, 8%, and ≤1.5% of the general population aged 10–19, 20–29, and ≥30 years, respectively, are still susceptible to HAV infection [Wu et al., 1980]. The age-specific prevalence of acute hepatitis B showed a similar trend to that of acute hepatitis A, also in keeping with the epidemiological background of HBV infection in Taiwan, where only 28%, 11%, and 5% of the general population aged 10–19, 20–29, and ≥30 years, respectively, are still susceptible to HBV infection [Sung et al., 1984].

Twenty-one percent of sporadic acute viral hepatitis

TABLE III. Serum GB virus-C/Hepatitis G Virus (GBV-C/HGV) RNA in Sporadic Acute Viral Hepatitis in Taiwan

Etiology	No. (%) with GBV-C/HGV RNA
Acute hepatitis A (n = 12)	0 (0%)
Acute hepatitis B (n = 17)	1 (5.9%)
Acute hepatitis C (n = 70)	8 (11.4%)
Acute hepatitis E (n = 5)	0 (0%)
Acute hepatitis non-A-E (n = 53)	2 (3.8%)
HBsAg carriers with	
Acute hepatitis A (n = 2)	0 (0%)
Acute hepatitis C (n = 35)	4 (11.4%)
Acute hepatitis D (n = 17)	1 (5.9%)
Acute hepatitis E (n = 6)	0 (0%)
Acute hepatitis C and D (n = 4)	0 (0%)
Acute hepatitis non-A-E (n = 58)	2 (3.4%)
Acute exacerbation of chronic hepatitis B (n = 55)	1 (1.8%)
Total (N = 334)	19 (5.7%)

cases in the present series could be attributed to acute hepatitis C. The incidence of acute hepatitis C was markedly higher than that of acute hepatitis A or B. The role of HCV in sporadic acute NANB hepatitis differs considerably with the geographical region. HCV accounted for 55% (70/128) of sporadic acute NANB hepatitis cases in this series (Table I), 55–60% of those in the United States [Alter et al., 1990], approximately 30% of those in Saudi Arabia, Greece, and Spain [Rodriquez et al., 1991; Tassopoulos et al., 1992; Ghabrah et al., 1995], and only 10–20% of those in China and India [Arankalle et al., 1993; Luo et al., 1994]. The present results also revealed that the age-specific prevalence of acute hepatitis C showed an inverse trend to that of acute hepatitis A or B (Fig. 1). Only about 8–12% of sporadic acute viral hepatitis cases aged 15–44 years could be attributed to acute hepatitis C. The prevalence of acute hepatitis C then increased significantly with increasing age, and reached to a peak of 42% in cases of age ≥65 years. It seems that most of the general population older than 40 years of age in Taiwan have been infected at some time by both HAV and HBV [Wu et al., 1980; Sung et al., 1984] and thus might be relatively more susceptible to HCV infection. Furthermore, the present results also showed a significantly higher prevalence of acute hepatitis C in females than in males. The reason for this sex difference remains unknown. Notably, a previous study from Singapore also showed that patients of acute NANB hepatitis had a significantly higher mean age and less male predominance than those of acute hepatitis A or B [Chan et al., 1981], and another study form the United States revealed that acute NANB hepatitis was found predominantly in the older women [Dienstag et al., 1977].

Only 1–2% of sporadic acute viral hepatitis cases in the present series could be attributed to acute hepatitis E, which accounted for 4% (5/128) of sporadic acute NANB hepatitis (Table I). At least two cases of acute hepatitis E in this series were HEV RNA positive by PCR (Chu et al., unpublished observation). None of these cases were associated with travel to endemic areas. The current data suggested that, although Taiwan is not an area endemic for HEV, sporadic cases of acute hepatitis E can occur and thus should be considered in the differential diagnosis of acute NANB hepatitis.

Sixteen percent of sporadic acute viral hepatitis cases in the present series did not demonstrate serological markers of HAV, HBV, HCV, HDV, or HEV infection, and were referred to as acute hepatitis non-A-E (Table I). The incidence of acute hepatitis non-A-E in the present series appears to be much higher than that of acute hepatitis A or B, and acute hepatitis non-A-E indeed is nearly as etiologically common as acute hepatitis C in Taiwan. Previous studies have revealed that some 4–40% of sporadic acute viral hepatitis cases in the United States, Europe, Asia, and Africa were associated with acute hepatitis non-A-E [Tsega et al., 1992; Arankalle et al., 1993; Buti et al., 1994; Luo et al., 1994; Ghabrah et al., 1995; Alter et al., 1997]. These findings suggested that at least one additional transmissible hepatitis agent might exist and is medically important, and that the putative agent or agents appeared to have a wide geographical range. The clinical and epidemiological features of acute hepatitis non-A-E need to be further characterized. Perhaps another interesting finding of the present study is that, unlike acute hepatitis C, the prevalence of acute hepatitis non-A-E in this series did not show any age or sex predominance (Table I and Fig. 1).

Two (3.8%) of 53 cases with acute hepatitis non-A-E in this series were GBV-C/HGV RNA positive. This figure is appreciably high when compared with the 1% prevalence rate of GBV-C/HGV viremia in the healthy adults in Taiwan [Kao et al., 1997b]. However, the proportion of patients with acute hepatitis non-A-E who were found to be positive for GBV-C/HGV RNA was similar to or lower than that of patients with acute hepatitis B, C, or D (see Table III). These findings are similar to those of previous observations from western countries [Dawson et al., 1996; Linen et al., 1996; Alter et al., 1997; Karayiannis and Thomas, 1997] and suggest that the role of GBV-C/HGV in acute hepatitis non-A-E in our geographical area is also limited, if any.

About 50–55% of sporadic acute viral hepatitis cases in the present series were chronic HBsAg carriers with acute exacerbation of chronic HBV infection or viral superinfection (Table I). These patients were first recognized as chronic HBsAg carriers because of positive HBsAg but negative IgM anti-HBc while presenting an episode of acute viral hepatitis. Serological markers of acute non-B hepatotropic virus infection were demonstrated in 36% (64/177) of these cases, with HCV being the most common, followed by HDV, HEV, and HAV, without any sex difference (Table II). The causes of acute hepatitis in the remaining cases might be related to acute exacerbation of chronic HBV infection or non-A-E virus superinfection. Notably, the role of GBV-C/HGV in these cases is also limited, if any (Table III).

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